

REMARKS

Upon entry of the foregoing amendments, claims 85 through 126 will be pending in this application. Claims 85, 92, 100, 107 and 120 are independent claims.

The specification has been amended by including a section containing cross-references to related applications, directly after the title at page 1. It is believed that these references are timely filed in accordance with 37 CFR 1.78(a)(2)(ii)(C), since the present application is a national phase application filed under 35 USC 371, based on an International application filed in English and designating the U.S. before November 29, 2000. The status of the parent application on which the International application was based has been updated, and reference was also made to the grandparent provisional application of the International application. Moreover, any delay between the present date when the Cross-Reference to Related Applications was included and a date four months from the filing date of the present application or 16 months from the priority date was unintentional. It is not believed that any additional fee for including these cross-references is necessary or that any additional statements are necessary in view of the previously cited 37 CFR 1.78(a)(2)(ii)(C). However, if the Examiner comes to an opposite conclusion, he is respectfully requested to contact the undersigned attorney and is authorized to charge any such fees to the undersigned attorney's law firm's Deposit Account 50-1017.

Specifically identified journal references were inserted into Examples 2 and 3 at page 30. These references are the same as set forth in the paragraph bridging pages 9 and 10, so no new matter has been added. The Examiner is respectfully requested to enter the amendments to the specification and to withdraw the objection to the specification at page 2, section 2 of the Detailed Action.

All prior claims were cancelled without prejudice, including claims 59-75 and 81-84, which were withdrawn from further consideration as being directed to a non-elected invention, where the cancellation is without prejudice to their inclusion in one or more related applications. The new claims are closely related to or supported by the prior claims as set forth in the following table:

New Claim	Prior Claim	New Claim	Prior Claim
85	38	104	42
86	39	105	43
87	40	106	53
88	41	107	54
89	42	108	39
90	43	109	40
91	45	110	41
92	44	111	42
93	39	112	43
94	40	113	New
95	41	114	New
96	42	115	55
97	43	116	56
98	46	117	76
99	48	118	77
100	52	119	79
101	39	120	57
102	40	121	39
103	41	122	41
		123	42
		124	43
		125	58
		126	80

In addition to the support set forth in the foregoing table, the claims are also supported in the application as noted below:

Claim 85, including aspects relating to the effect of the antimicrobial composition on cell membranes, is supported, for instance, in Example 14, bridging pages 38 and 39, and also in the paragraphs bridging pages 40 and 41.

Claim 98 is supported by the disclosure at page 14, last paragraph of the application.

Claim 113 is supported in the application at page 3, line 33; page 19, lines 6-8; page 27, lines 26-31; and page 43, lines 17-20, among other locations.

Claim 114 is supported in the application at page 44, lines 7-11, and page 46, lines 27-30, among other locations.

Claim 116 is supported at least by disclosure in the application at page 44, line 21, through page 46, line 21.

No new matter has been added by any of the amendments. Accordingly, entry of the new claims is respectfully solicited.

Claims 44 and 50-56 have been objected to as depending from rejected claims. As noted above and in the foregoing table, independent claims 92, 100, and 107 are independent claims and correspond to objected to claims 44, 52 and 54, respectively, and accordingly, should now be allowable. Dependent claims 93-99 depend directly or indirectly from claim 92 and should be allowable. Dependent claims 101-106 (where claim 106 corresponds to objected to claim 53) depend directly or indirectly from claim 100 and should be allowable. Dependent claims 108-119 (where claims 115 and 116 generally correspond to objected to claims 55 and 56, respectively) depend directly or indirectly from claim 107 and should be allowable.

Claims 87, 94, 102 and 109, each of which was based on prior claim 40, recite that the histone H1 protein is covalently linked with polyethylene glycol. This is supported in the paragraph bridging pages 10 and 11. Claim 40 had been rejected as being indefinite under 35 USC 112, second paragraph, due to the prior use in claim 40 of the term "derivated." It is believed that this rejection is moot in view of claims 87, 94, 102 and 109. Accordingly, reconsideration and withdrawal of the rejection relating to claim 40 to the extent that such rejection may be considered applicable to claims 87, 94, 102 and 109 are respectfully solicited.

Prior method claims 76-80 were also rejected under 35 USC 112, second paragraph, as being incomplete for omitting essential details, apparently how the composition is attached to the surface and which coupling group is involved. Method claims 76-80 have been cancelled in favor of claims 117-119 (medical device) and claims 120-126 (wrap of synthetic polymer for perishable food). Since these claims are no longer method claims, it is believed that any rejections based on method steps are moot. Accordingly, reconsideration and withdrawal of the rejections to the extent that they may be applied to claims 117-126 are respectfully solicited.

Claims 46-48, directed to kits, were rejected, based on the Examiner's conclusion that the term "instructional material" was too indefinite. New claims 98 and 99 are directed to kits and correspond to prior claims 46 and 48, respectively. However, claims 98 and 99 do not contain any recitation of instructional material. Accordingly, the rejection of claims 46-48 is moot with respect to claims 98 and 99.

Claims 57 and 57 were rejected for their recitation of a "biological macromolecule," which the Examiner determined to be indefinite. New claims 120 and 125 continue to refer to a

biological macromolecule. Applicants respectfully submit that even without a specific identification of which biological macromolecules are particularly involved, the term is not indefinite, in view of the generally accepted definition of a biological macromolecule as the term would be understood by one skilled in this art. "Macromolecule" is defined in *Dorland's Illustrated Medical Dictionary*, 1994, Edition 28, W.B. Saunders Company, p. 977, as "a very large molecule having a polymeric chain structure, as in proteins, polysaccharides, and other natural and synthetic polymers." To distinguish synthetic polymers and potential inorganic macromolecules from those of interest in the present invention, "biological" was used as an adjective as referring to molecules associated with living organisms, such as proteins, polysaccharides, and other natural polymers found in the body. See *Dorland's Illustrated Medical Dictionary*, p. 199, for example, with respect to the definition of biological and biology. Reconsideration and withdrawal of the rejection as it may be applied to claims 120 and 125 are respectfully solicited.

The Examiner rejected claims 38, 39, 41, 42, 45 and 49 under 35 USC 102(b) as being anticipated by Zeppezauer *et al.* U.S. Patent 5,182,257 (the "'257 patent'"), citing column 7, lines 41-60 and claim 6, which the Examiner characterized as teaching "a composition which comprises only one listed constituent, *i.e.*, pure histone H1 and a physiologically acceptable carrier." Claim 85, which corresponds to prior claim 38, relates to an antimicrobial composition having the designated antibiotic activity now set forth in claim 85. The '257 patent, as set forth in the last paragraph of column 1 and the first paragraph of column 2, make it clear that the histone compositions, including histone H1, "or at least a partial section of at least five amino acid residues of the evolutionary variable histone section (amino-acid residues 1 to 30) of the histones" are used as "a hormonal or hormone-like active substance for the preparation of pharmaceuticals used in immunotherapy, the therapy of endocrine disturbances and in cancer therapy," according to the last paragraph of column 1.

The first paragraph of column 2 of the '257 patent relates to use of the histone product for:

the treatment of cancer and radiation induced leukemia,
AIDS-diseases, for dampening the function of the
suprarenal cortex, the thyroid, of the gonads, for supporting
the function of the hypophysis and for the treatment of
after-effects resulting from the removal of the thymus gland
(thymectomy).

Claims 38, 39, 41-43 and 45 were rejected under 35 USC 102(b) as being anticipated by Zeppezauer U.S. Patent 5,578,571 ("the '571 patent"), based on the Examiner's conclusion that it teaches a composition "which comprises \geq H1, H2A, H2b, and a therapeutically acceptable carrier (claim 1)." What the Examiner did not indicate, but what is included throughout the '571 patent, and even in independent claims 1 and 3, is that the prior art invention does not contain any of the histones alone, but rather, it contains the indicated histones in combination with other drugs, such as vincristin, to have a synergistic therapeutic effect on lymphoma cells (claim 1), or with methotrexate or cisplatin to have a synergistic therapeutic effect on melanoma cells (claim 3). See also, for example, the object of the invention set forth at column 1, lines 37-48, of the '571 patent relating to the chemotherapeutic use of combinations of drugs, and typically the cytostatic drugs, such as the three mentioned above.

Although the '257 patent claims a biologically active composition comprising a physiologically acceptable carrier and pure histone H1, and the '571 patent discloses use of combinations of at least one histone, which may be H1, and other cytostatic drugs, both patents are remarkable for what they do not teach. They do not teach any antibiotic activity whatsoever for histones, including histone H1, either in an antimicrobial composition as a single active ingredient or in combination another antimicrobial composition with other active ingredients.

If histone H1 had been recognized as providing any type of antibiotic activity, it would have been mentioned in the cited references. Instead, no such activity was mentioned because antibiotic or antimicrobial activity for histone H1 was not discovered until approximately 14 years after the different therapeutic uses mentioned in the '257 patent, which issued on an application filed in 1985. None of the inventors of the inventions disclosed in the '257 and '571 patents, including Michael Zeppezauer, one of the inventors of the invention claimed in the present application, knew in 1985 that histones could have an antibiotic effect against prokaryotic cells, especially bacteria, until its discovery as noted and acknowledged in U.S. Patent 6,565,854, which issued on the priority application to the present application.

The Examiner is respectfully urged to reconsider and withdraw the anticipation rejections of the prior claims to the extent that they may be made with respect to claim 85 and any claim depending from claim 85. The references must be considered as a whole for what they teach, and also for what they do not teach. Here, it is clear that the references do not teach what is claimed in the present application, namely, an antimicrobial composition comprising a

eukaryotic histone H1 protein having the antibiotic activity recited in claim 85. The prior art cited by the Examiner simply does not teach or even suggest such an antimicrobial composition.

In the copy of the Information Disclosure Statement by Applicant, Form PTO/SB/08A, initialed and signed by the Examiner and attached to the Office Action, German patent document 197 15 149 A1 (hereinafter "Foreign Reference") was lined through and not initialed by the Examiner, apparently because it is not in the English language, since there was no indication that the reference was not received. The Foreign Reference was cited in the English language International Search Report from the PCT application, corresponding to the present application. A copy of the International Search Report is attached hereto, in the form of the PCT application International Publication No. WO 01/10901 A3, which was published with the International Search Report on August 9, 2001. The relevance of the Foreign Reference is noted on page 1 of 2 of the International Search Report. According to MPEP Section 609 III A(3) (page 600.122), this is a sufficient description of the Foreign Reference, and the Examiner is therefore required to consider this foreign language reference. A copy of this portion of the MPEP, highlighted for the Examiner's convenience, is attached hereto. Consideration and citation of the Foreign Reference, and an acknowledgment of such consideration in the next Office Action are therefore respectfully requested. It is not believed that it is necessary to make any additional payments for this consideration, but if the Examiner determines otherwise, he is requested to contact the undersigned attorney and may charge any required fee to the undersigned attorney's law firm's Deposit Account 50-1017.

It is noted that the Foreign Reference corresponds to WO 9846252A, published October 22, 1998, as indicated in the International Search Report Information on Patent Family Members attached to the International Search Report. Also attached is a copy of a two page bibliography of WO 9846252A, which is the publication number for the corresponding International Patent Application No. PCT/EP98/02112. An additional attachment is a copy of U.S. Patent Publication No. US 2003/0017987 A1, which is a continuation of U.S. Patent Application No. 09/402,468, which is a 35 USC § 371 application based on International Patent Application No. PCT/EP98/02112. Accordingly, the written description of the U.S. Patent Publication No. US 2003/0017987 A1 should be substantially identical to the International Application and to the Foreign Reference. As a result of these corresponding applications, the Examiner is respectfully requested to consider the U.S. Patent Publication No. US 2003/0017987 A1 as the equivalent of

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the Foreign Reference. Again, it is not believed that it is necessary to make any additional payments for this consideration, but if the Examiner determines otherwise, he is requested to contact the undersigned attorney and may charge any required fee to the undersigned attorney's law firm's Deposit Account 50-1017.

Reconsideration and withdrawal of all objections and rejections, and an early Notice of Allowance of all claims are respectfully solicited.

Respectfully submitted,

REINER CLASS *et al.*

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Bibliographic pages 1 and 2 regarding WO98/46252

U.S. Patent Publication No. US 2003/0017987 A1